

CLINICAL STUDY PROTOCOL

A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous Sulbactam-ETX2514 in the Treatment of Hospitalized Adults With Complicated Urinary Tract Infections, Including Acute Pyelonephritis

Investigational Product: ETX2514SUL

Protocol Number: CS2514-2017-0003

EudraCT Number: 2017-002608-29

Sponsor:

[REDACTED]
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SIGNATURE PAGE

STUDY TITLE: A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous Sulbactam-ETX2514 in the Treatment of Hospitalized Adults With Complicated Urinary Tract Infections, Including Acute Pyelonephritis

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature

Date

[REDACTED]

[REDACTED]

[REDACTED]

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by ██████████ to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to ██████████ and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by ██████████, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

Investigator's Signature

Date

Investigator's Printed Name

SYNOPSIS

TITLE: A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous Sulbactam-ETX2514 in the Treatment of Hospitalized Adults With Complicated Urinary Tract Infections, Including Acute Pyelonephritis

PROTOCOL NUMBER: CS2514-2017-0003

INVESTIGATIONAL PRODUCT: Sulbactam-ETX2514 (ETX2514SUL)

PHASE: 2

INDICATION: Patients with complicated urinary tract infection (cUTI), including acute pyelonephritis (AP)

OBJECTIVES:

The primary objective of this study is to evaluate the safety profile of ETX2514SUL versus placebo in patients with cUTI, including AP.

The secondary objectives of this study are the following:

- To evaluate the efficacy of ETX2514SUL in patients with cUTI, including AP, in the microbiologically modified Intent-to-Treat (m-MITT) Population;
- To compare the clinical cure rate in the 2 treatment groups in the modified Intent-to-Treat (MITT), m-MITT, Clinical Evaluable (CE), and Microbiological Evaluable (ME) Populations at the Test-of-Cure (TOC) Visit; and
- To compare the microbiological eradication rate in the m-MITT and ME Populations at the TOC Visit.

The exploratory objective of this study is to evaluate the efficacy of ETX2514SUL against cUTIs caused by *Acinetobacter baumannii* and by pathogens susceptible to imipenem plus ETX2514SUL but resistant to imipenem in the m-MITT Population.

POPULATION:

The population for this study is approximately 80 hospitalized adult patients with cUTI, including AP. At least 30% of patients will have a diagnosis of AP at study entry.

INCLUSION CRITERIA:

Patients who meet all of the following criteria will be eligible to participate in the study:

1. A signed informed consent form (ICF). If a study patient is unable to provide informed consent due to their medical condition, the patient's legally authorized representative may consent on behalf of the study patient as permitted by local law and institutional Standard Operating Procedures;
 2. Male or female, 18 to 90 years of age, inclusive;
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3. Expectation, in the judgment of the Investigator, that the patient's cUTI would require initial hospitalization and treatment with intravenous (IV) antibiotics;
 4. Documented or suspected cUTI or AP, as defined below:
 - cUTI
 - Signs or symptoms evidenced by at least 2 of the following:
 - Documented fever accompanied by chills, rigors, or warmth;

Note: fever must be observed and documented by a health care provider within 24 hours of Screening (oral, tympanic, rectal, or core temperature $>38^{\circ}\text{C}$ [$>100.4^{\circ}\text{F}$]).
 - Nausea or vomiting within 24 hours of Screening, as reported by the patient;
 - Dysuria, increased urinary frequency, or urinary urgency; or
 - Lower abdominal pain, pelvic pain, or suprapubic tenderness on physical examination;
 - *And* urine specimen with evidence of pyuria:
 - Positive leukocyte esterase on urinalysis; or
 - White blood cell count ≥ 10 cells/ mm^3 in unspun urine; or
 - White blood cell count ≥ 10 cells/high-power field (hpf) in urine sediment;
 - *And* at least 1 of the following associated risks:
 - Use of intermittent bladder catheterization or presence of an indwelling bladder catheter;

Note: indwelling bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of the Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated.
 - Current known functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a post-void residual urine volume of ≥ 100 mL;
 - Complete or partial obstructive uropathy (eg, nephrolithiasis, tumor, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to End of Treatment [EOT]);
 - Azotemia, defined as blood urea nitrogen >20 mg/dL, blood urea >42.8 mg/dL, or serum creatinine >1.4 mg/dL, due to known prior intrinsic renal disease; or
 - Chronic urinary retention in men (eg, previously diagnosed benign prostatic hypertrophy);
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- AP
 - Signs or symptoms evidenced by at least 2 of the following:
 - Documented fever accompanied by chills, rigors, or warmth;

Note: fever must be observed and documented by a health care provider within 24 hours of Screening (oral, tympanic, rectal, or core temperature >38°C [$>100.4^{\circ}\text{F}$]).
 - Nausea or vomiting within 24 hours of Screening, as reported by the patient;
 - Dysuria, increased urinary frequency, or urinary urgency; or
 - Acute flank pain (onset within 7 days prior to randomization) or costo-vertebral angle tenderness on physical examination;
 - *And* urine specimen with evidence of pyuria:
 - Positive leukocyte esterase on urinalysis; or
 - White blood cell count ≥ 10 cells/mm³ in unspun urine; or
 - White blood cell count ≥ 10 cells/hpf in urine sediment;
5. Have a baseline urine culture specimen obtained within 48 hours prior to randomization;

Note: patients may be randomized into this study and start IV study drug therapy before the Investigator knows the results of the baseline urine culture.
 6. Expectation, in the judgment of the Investigator, that any implanted urinary instrumentation (eg, nephrostomy tubes, ureteric stents) will be surgically removed or replaced before or within 24 hours after randomization, unless removal or replacement is considered unsafe or contraindicated;

Note: temporary bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated.
 7. Expectation, in the judgment of the Investigator, that the patient will survive with effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study;
 8. Women of childbearing potential (ie, not post-menopausal or surgically sterilized) must have a negative pregnancy test (serum or urine) before randomization. Participating women of childbearing potential must be willing to consistently use 2 highly effective methods of contraception (ie, condom plus spermicide, combined oral contraceptive, implant, injectable, indwelling intrauterine device, or a vasectomized partner) from Screening until at least 30 days after administration of the last dose of study drug; and
 9. Male participants will be required to use condoms with a spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug.
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EXCLUSION CRITERIA:

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Presence of any known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy, including but not limited to the following:
 - Perinephric abscess;
 - Renal corticomedullary abscess;
 - Uncomplicated urinary tract infection (UTI);
 - Any recent history of trauma to the pelvis or urinary tract;
 - Polycystic kidney disease;
 - Chronic vesicoureteral reflux;
 - Previous or planned renal transplantation;
 - Patients receiving dialysis, including hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration;
 - Previous or planned cystectomy or ileal loop surgery; and
 - Known or suspected infection that is caused by a pathogen(s) that is known to be resistant to imipenem or β -lactam/ β -lactamase inhibitor combinations, including infection caused by fungi (eg, candiduria) or mycobacteria (eg, urogenital tuberculosis);
2. Presence of suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination;
3. Gross hematuria requiring intervention other than administration of study drug or removal or exchange of a urinary catheter;
4. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy prior to EOT);
5. Renal function at Screening as estimated by creatinine clearance <70 mL/min using the Cockcroft-Gault formula and serum creatinine value obtained from a local laboratory;
6. Known non-renal source of infection such as endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to randomization that would interfere with evaluation of response to the study antibiotics;
7. Any signs of severe sepsis, including but not limited to the following:
 - Shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline (if known) that is not responsive to fluid challenge; or
 - Disseminated intravascular coagulation as evidenced by prothrombin time or partial thromboplastin time $\geq 2 \times$ the upper limit of normal (ULN) or $<50,000$ platelets/mm³ at Screening in patients in whom severe sepsis is suspected;

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8. Pregnant or breastfeeding women;
 9. Known seizure disorder requiring current treatment with anti-seizure medication which, in the opinion of the Investigator, would prohibit the patient from complying with the protocol. Patients with a history of epilepsy or who are on stable treatment (ie, no change in therapy within 30 days) with well controlled seizure disorder (ie, no recurrent episodes in the past 30 days) may be considered for enrollment in the study;
 10. Treatment within 30 days prior to randomization with any cancer chemotherapy, immunosuppressive medications for transplantation, or medications for rejection of transplantation;
 11. Patient requires continuing treatment with probenecid, methotrexate, ganciclovir, valproic acid, or divalproex sodium during the study;
 12. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy;
 13. Aspartate aminotransferase or alanine aminotransferase $>3 \times \text{ULN}$ or total bilirubin $>2 \times \text{ULN}$ at Screening;
 14. Receipt of a single dose of a long-acting, potentially-effective systemic antibiotic with activity against Gram-negative uropathogens for more than 24 hours within the 72-hour window prior to randomization. However, patients may enroll who:
 - Have received >48 hours of prior antimicrobial therapy, and (1) in the opinion of the Investigator, have failed that preceding antimicrobial therapy (ie, have worsening signs and symptoms), and (2) are documented to have a cUTI or AP that is caused by a pathogen resistant to the prior therapy, and (3) the causative pathogen is known not to be resistant (eg, the causative pathogen is either susceptible, intermediate, or unknown susceptibility) to imipenem;
 - Develop signs and symptoms of cUTI or AP while taking a systemic antibiotic for another indication (other than ETX2514SUL or imipenem/cilastatin), including antimicrobial prophylaxis for recurrent UTI; or
 - Received a single dose of a short-acting (ie, having a dosage frequency of more than once daily [eg, every 12 hours or more frequently]) systemic antibiotic up to 24 hours prior to randomization. No more than 25% of patients will be enrolled who meet this criterion;
 15. Requirement at time of randomization for any reason for additional systemic antimicrobial therapy (including antibacterial, antimycobacterial, or antifungal therapy) other than study drug, with the exception of a single oral dose of any antifungal treatment for vaginal candidiasis;
 16. Likely to require the use of an antibiotic for cUTI or AP prophylaxis during the patient's participation in the study (from randomization through the Late Follow-up [LFU] Visit);
 17. Known history of human immunodeficiency virus infection and known recent CD4 count $<200/\text{mm}^3$ within the last year;
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18. Presence of significant immunodeficiency or an immunocompromised condition, including hematologic malignancy, bone marrow transplant, or receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (equivalent to ≥ 20 mg/day of prednisone or systemic equivalent for ≥ 2 weeks);
 19. Presence of neutropenia (absolute neutrophil count $< 1000/\text{mm}^3$) obtained from a local laboratory at Screening;
 20. Presence of thrombocytopenia (especially in patients diagnosed with disseminated intravascular coagulation or at risk of serious bleeding) $< 50,000$ platelets/ mm^3 obtained from a local laboratory at Screening;
 21. A QT interval corrected using Fridericia's formula > 480 msec;
 22. History of significant hypersensitivity or allergic reaction to any β -lactam, any contraindication to the use of imipenem/cilastatin based on local approved prescribing information (eg, Summary of Medicinal Product Characteristics), any contraindication to the excipients used in the respective formulations, or any contraindication to the use of β -lactam antibiotics;
 23. Participation in a clinical study involving investigational medication or an investigational device within the last 30 days or 5 half-lives, whichever is longer, prior to randomization;
 24. Unable or unwilling, in the opinion of the Investigator, to comply with the protocol; or
 25. Any patients previously randomized in this study.
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STUDY DESIGN AND DURATION:

This study is a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of IV ETX2514SUL in patients with cUTIs who are otherwise relatively healthy. Patients providing informed consent and meeting all study eligibility criteria will be enrolled in the study and have a pre-treatment urine and blood sample obtained and submitted to the local laboratory. Approximately 80 patients will be randomized 2:1 to receive either 1 g ETX2514/1 g sulbactam IV or matching placebo every 6 hours (q6h). All patients will receive background therapy with 500 mg IV imipenem/cilastatin q6h. Randomization will be stratified by baseline diagnosis (symptomatic cUTI versus AP). At least 30% of patients will have a diagnosis of AP at study entry.

Receipt of any long-acting, potentially-effective systemic antibiotic with activity against Gram-negative uropathogens for more than 24 hours within the 72-hour window prior to randomization is prohibited. However, patients who have received a single dose of a short-acting systemic antibiotic up to 24 hours prior to randomization may be randomized up to a maximum of 25% of the study enrollment. A short-acting antibiotic is defined as having a dosage frequency of more than once daily (eg, every 12 hours or more frequently).

Any organism isolated from the blood or urine cultures will be identified by genus and species by the local laboratory. Urine organisms will be cultured and quantified at the local laboratory, and susceptibility of the organism(s) may be performed per local laboratory standards. All baseline urine organisms that grow $\geq 10^5$ colony-forming units (CFU)/mL and not deemed to be a contaminant, as detailed in the Microbiology Procedures Manual, are to be sent from the local

laboratory to the central laboratory. Potential pathogens that grow in both the urine and blood will also be sent to the central laboratory prior to randomization.

For post-baseline urine cultures, only those potential pathogens that grow at $\geq 10^3$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory.

All blood organism(s) cultured at the local laboratory from blood samples (whether at baseline or post-baseline) and not deemed to be a contaminant per the Microbiology Procedures Manual will be sent to the central laboratory for confirmation of identification and susceptibility testing.

Although local susceptibility testing is not a requirement, when local susceptibility testing indicates non-susceptibility to imipenem (eg, intermediate susceptibility or resistance to imipenem) but the patient is stable or clinically improving, the patient should remain on study drug at the discretion of the Investigator. Prior to discontinuation from study drug, the Investigator should discuss such cases with the Medical Monitor.

Day 1 is defined as the first day of study drug administration. The subsequent study days are defined by the number of calendar days thereafter. The duration of antibiotic treatment with study drug therapy will be 7 days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

All patients should receive at least 8 doses of IV study drug before the Investigator considers the patient to be a clinical failure and discontinues the patient from study drug therapy. No oral switch option is allowed. Patients who withdraw from study drug dosing should perform all EOT Visit procedures and should be followed through the LFU Visit for safety assessments, even if they withdraw from dosing due to clinical failure.

Throughout the study, all patients will be monitored for signs and symptoms of cUTI or AP and the occurrence of adverse events. Laboratory data, including chemistry panels, complete blood counts, and samples for urine and blood cultures, as well as electrocardiograms (ECGs), will be collected from all patients at specified times throughout the study.

Sparse pharmacokinetic (PK) sampling (ie, a total of 5 samples per patient) will be performed to refine the population PK model. To maintain the blind, PK samples will be collected from both treatment groups. Samples obtained from the ETX2514SUL group will be analyzed using a validated assay by a central bioanalytical laboratory.

Patients will be enrolled in the study for approximately 21 days, with a maximum duration of study participation of 30 days. Screening procedures can be performed as standard of care within 48 hours prior to randomization on Day 1, with the exception of local laboratory serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. The Treatment Period begins on Day 1, and study drug will be administered for 7 calendar days (or up to 14 days in patients with concurrent bacteremia). The EOT Visit will be completed on the final dosing day or the following day (allowing for a 1-day window to complete EOT procedures). The Test-of-Cure (TOC) Visit will be completed 7 days (± 1 day) after the EOT for all patients. The LFU Visit will be completed 7 days (± 2 days) after the TOC Visit for all patients.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The following study drugs will be administered q6h in a double-blind manner:

- 1 g ETX2514/1 g sulbactam IV administered q6h over 3 hours, or
- Matching placebo IV administered q6h over 3 hours.

In addition, all patients will be administered background therapy with 500 mg IV imipenem/cilastatin q6h infused over 30 minutes. Infusions of study drug will occur q6h for 7 calendar days, with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

EFFICACY VARIABLES:

The primary efficacy parameter is the proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the TOC Visit.

The secondary efficacy parameters include the following:

- Proportion of patients with a response of clinical cure in the MITT, m-MITT, CE, and ME Populations at the TOC Visit; and
- Proportion of patients with a response of microbiologic eradication in the m-MITT and ME Populations at the TOC Visit.

The exploratory efficacy parameters include the following:

- Proportion of patients with a response of sustained microbiologic eradication in the m-MITT and ME Populations at the LFU Visit;
- Proportion of patients with a response of sustained clinical cure in the MITT, m-MITT, CE, and ME Populations at the LFU Visit;
- Proportion of patients with a response of clinical cure in the MITT and m-MITT Populations at Day 5;
- All-cause mortality through the LFU Visit in the MITT Population;
- Summary (number and percentage of patients) of the assessment of clinical signs and symptoms of cUTI and AP at each time point throughout the study by treatment group in the MITT Population; and
- Descriptive statistics of the length of hospital stay by treatment group for the MITT Population.

Outcome Definitions:

Overall Response:

Overall success: a patient deemed a clinical cure AND who achieved microbiologic eradication.

Overall failure: a patient deemed a clinical failure OR deemed to have microbiological persistence.

Overall indeterminate: insufficient data are available to determine if the patient is an overall success or failure.

Clinical Outcome (at the Day 5, EOT, and TOC Visits):

Clinical cure: complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted.

Clinical failure: symptoms of cUTI or AP present at study entry have not significantly improved or completely resolved, or new symptoms of cUTI or AP have developed and require the initiation of a non-study antibacterial drug therapy, or death.

Clinical indeterminate: insufficient data are available to determine if the patient is a cure or failure.

Clinical Outcome (at the LFU Visit):

Sustained clinical cure: met criteria for clinical cure at the TOC Visit and the LFU Visit.

Relapse: clinical cure at the TOC Visit but signs and symptoms of cUTI or AP are present at the LFU Visit.

Clinical failure: clinical failure at the TOC Visit carried forward to the LFU Visit or death between the TOC Visit and LFU Visit.

Clinical indeterminate: insufficient data are available to determine if the patient is a sustained clinical cure or clinical relapse.

Microbiologic Outcome (at the Day 5, EOT, and TOC Visits):

Microbiologic eradication: the demonstration that the baseline bacterial pathogen(s) is reduced to $<10^4$ CFU/mL according to the Food and Drug Administration (FDA) criteria and $<10^3$ CFU/mL according to the European Medicines Agency (EMA) criteria on urine culture and negative on repeat blood culture (if positive at baseline).

Microbiologic persistence: the urine culture grows $\geq 10^4$ CFU/mL for the FDA ($\geq 10^3$ CFU/mL for the EMA) of any of the baseline pathogen(s) identified at study entry and/or a blood culture demonstrates the same baseline pathogen(s). Patients who are a persistence at EOT will be considered a persistence at TOC.

Microbiologic indeterminate: no follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated. For a baseline blood pathogen, no follow-up blood culture is available.

Microbiologic Outcome (at the LFU Visit):

Sustained microbiologic eradication: microbiologic eradication at the TOC Visit and the LFU Visit.

Presumed sustained microbiologic eradication: no urine culture was done at LFU and patient meets clinical criteria for sustained clinical cure.

Microbiologic recurrence: urine culture grows $\geq 10^4$ CFU/mL for the FDA ($\geq 10^3$ CFU/mL for the EMA) of any of the baseline pathogen(s) identified at study entry and/or a positive blood culture at any time after documented eradication at the TOC Visit up to and including the LFU Visit.

Microbiologic continued persistence: a per-pathogen microbiologic outcome of persistence at the TOC Visit will be considered a continued persistence.

Microbiologic indeterminate: no follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated and the patient is not a sustained clinical cure.

SAFETY VARIABLES:

The safety parameters include the incidence, severity, causality, and seriousness of treatment-emergent adverse events (TEAEs) and the evaluation of changes from baseline in safety laboratory test results, ECGs, vital signs, and physical examinations.

STATISTICAL ANALYSES:**Efficacy:**Primary:

The number and percentage of patients in each treatment group with an overall success, failure, and indeterminate response will be determined. A 2-sided 95% confidence interval (CI) for the observed difference in the overall success rates (ETX2514SUL group minus placebo group [background imipenem/cilastatin therapy]) will be calculated using a continuity-corrected Z-statistic.

Secondary:

The number and percentage of patients in each response category for each of the secondary efficacy outcomes will be provided. Two-sided 95% CIs for the difference in outcome rates between the ETX2514SUL group and the placebo group (background imipenem/cilastatin therapy) will be provided.

Pharmacokinetics:

Pharmacokinetic characterization and evaluation of serum exposures of ETX2514SUL in the PK Population will be performed using both non-compartmental and modeling methods. Using a sparse sampling approach, PK samples will be obtained from patients treated with ETX2514SUL or placebo prior to the first dose of study drug on Day 1 (1 sample pre-dose) and at 4 additional time points post-dose on Day 4 (± 1 day) (4 time points post-dose). The PK samples will be collected for both treatment groups to maintain the blind. The PK samples obtained from the ETX2514SUL group will be analyzed using a validated assay by a central bioanalytical laboratory.

Safety:

All patients who receive any amount of study drug (Safety Population) will be included in the safety analyses. Patients who received the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received.

Adverse events will be coded using version 20.0 (or higher) of the Medical Dictionary for Regulatory Activities. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a TEAE for each unique system organ class and preferred term will be tabulated. A TEAE is defined as an adverse event occurring on or after the administration of the first dose of study drug. Treatment-emergent adverse events will also be tabulated by treatment group, severity, and the relationship to study drug as assessed by the Investigator. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a treatment-emergent serious adverse event will be tabulated. The number and percentage of

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
<i>A. baumannii</i>	<i>Acinetobacter baumannii</i>
ALT	Alanine aminotransferase
AP	Acute pyelonephritis
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BL/BLI	β -lactam/ β -lactamase inhibitor
CE	Clinical Evaluable
CFR	Code of Federal Regulations
CFU	Colony-forming units
CI	Confidence interval
CRA	Clinical research associate
CTA	Clinical trial authorization
cUTI	Complicated urinary tract infection
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End of Treatment
ETX2514SUL	Sulbactam-ETX2514
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hpf	High-power field
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LFT	Liver function test
LFU	Late Follow-up
MAD	Multiple ascending doses
MDR	Multi-drug resistant
ME	Microbiologic Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibition concentration
MITT	Modified Intent-to-Treat
m-MITT	Microbiologically modified Intent-to-Treat

Abbreviation	Definition
PD	Pharmacodynamic
PK	Pharmacokinetics
q6h	Every 6 hours
QTcF	QT interval corrected using Fridericia's formula
SAD	Single ascending doses
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TOC	Test-of-Cure
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection

1 INTRODUCTION AND BACKGROUND INFORMATION

Acinetobacter baumannii (*A. baumannii*) is a nonfermenting Gram-negative bacteria that is increasingly being recognized as an important cause of severe infections, particularly in compromised hospitalized patients. It is a significant public health concern and is classified as a “serious threat” pathogen in the recent United States (US) Centers for Disease Control and Prevention “Antibiotic Resistance Threats” report¹ and is ranked as “critical” on the World Health Organization Priority Pathogens List for Research and Development of New Antibiotics.²

A. baumannii causes severe infections, which are associated with high mortality. Approximately 2% of healthcare-associated infections are caused by *A. baumannii*.³ Patients on mechanical ventilators and those with central line-catheters have the highest proportion of infections caused by *A. baumannii*. Serious infections including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, complicated urinary tract infections (cUTIs), bloodstream infections, and wound infections caused by *A. baumannii* are estimated to occur in 70,000 to 90,000 patients in the US per year, of which approximately 63% are caused by multi-drug resistant (MDR) isolates.⁴ Multi-drug resistance in *A. baumannii* is an evolving problem, with some countries in Europe reporting carbapenem-resistance rates >50%.⁵ Mortality associated with bacteremia and pneumonia caused by *A. baumannii* range from 30% to 50%.^{6,7} The risk of death associated with infections caused by *A. baumannii* isolates resistant to carbapenems is even higher.^{1,7} As a consequence of this extensive resistance, there is an urgent unmet medical need to identify new agents to treat *A. baumannii* infections.

A. baumannii has a number of resistance mechanisms that can be utilized and/or acquired. Among the most important of these are the production of β -lactamases, which degrade β -lactam antimicrobials. Contemporary *A. baumannii* isolates generally contain at least 1, and up to 5, β -lactamase gene;⁸ expression of class D β -lactamase is ubiquitous, but class A and/or extended spectrum class C expression is also common.

1.1 Nonclinical Experience with ETX2514

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1.2 Clinical Experience with ETX2514

A summary of clinical experience is provided in more detail in the Investigator's Brochure.

ETX2514 has been evaluated either alone or in combination with sulbactam and/or imipenem/cilastatin in a Phase 1 first-in-human study. This study evaluated single ascending doses (SAD) and multiple ascending doses (MAD) of ETX2514 to fully characterize the safety and PK profile of ETX2514. In addition, this study evaluated if there was any clinically significant drug-drug interaction between sulbactam and ETX2514. Since the activity of ETX2514SUL is targeted specifically at *A. baumannii*, ETX2514SUL will generally be given in combination with broader spectrum antimicrobials such as carbapenems. The use of ETX2514SUL co-administered with imipenem/cilastatin, a widely used carbapenem, has been evaluated in a drug-drug interaction study as a probe for potential interactions with other β -lactam antimicrobials.

ETX2514SUL was generally well tolerated in the SAD and MAD components of the Phase 1 study. There was no drug-drug interaction (2-way) when ETX2514 was co-administered with sulbactam, when ETX2514 was co-administered with imipenem/cilastatin, or when ETX2514 was co-administered with sulbactam and imipenem/cilastatin. The general adverse experience profile of ETX2514 was unchanged when co-administered, as a single dose, with sulbactam, with imipenem/cilastatin, and with sulbactam and imipenem/cilastatin.

1.3 Rationale

██████████ is developing ETX2514SUL, a novel bactericidal β -lactam/ β -lactamase inhibitor (BL/BLI) combination, for the treatment of serious infections caused by *A. baumannii*.

ETX2514 is a novel, rationally designed diazabicyclooctenone inhibitor. It is a potent inhibitor of class A and class C β -lactamases and is a broad-spectrum inhibitor of class D β -lactamases; ETX2514's coverage of all 3 classes is important because *A. baumannii* generally expresses class D β -lactamases in combination with class A and/or class C β -lactamases. ETX2514 is not a β -lactam. It displays a covalent, reversible mechanism of inhibition through β -lactamase active-site serine carbamoylation. ETX2514 exhibits intrinsic activity against some *Enterobacteriaceae* but has no significant clinical activity against *A. baumannii*.

Sulbactam is a penicillin derivative and is used widely as an inhibitor of β -lactamases. Although sulbactam is available as a standalone product in a small number of countries (eg, CombactamTM, Germany), the vast majority of human use is in combination with β -lactams (eg, UnasynTM, combination ampicillin/sulbactam). Unasyn is approved by regulatory authorities in the US, Europe, and the Asia-Pacific region. Sulbactam possesses intrinsic antimicrobial activity against *A. baumannii*; however, increasing resistance of *A. baumannii* to sulbactam has reduced its usefulness in treating infections caused by this bacterium.

This is a Phase 2, multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of intravenous (IV) ETX2514SUL plus imipenem/cilastatin compared to

imipenem/cilastatin alone in the treatment of hospitalized adults with cUTI, including acute pyelonephritis (AP).

1.4 Risk/Benefit

No unique contraindications have been determined for ETX2514. Contraindications to the use of sulbactam include a history of hypersensitivity or allergic reactions to sulbactam or any cephalosporin, penicillin, or carbapenem.

In the Phase 1 study in healthy subjects, ETX2514 was generally well tolerated in single doses ranging from 0.25 g to 8 g, in multiple doses ranging from 0.25 g to 2 g administered every 6 hours (q6h) for 8 days (29 doses), and in single dose drug-drug interaction studies with sulbactam, and with sulbactam and imipenem/cilastatin. There was no consistent pattern of local infusion site reactions to suggest a specific concern. The most common (occurring in $\geq 5\%$ of subjects) treatment-emergent adverse events (TEAEs) reported were headache, catheter site phlebitis, dizziness, and upper respiratory tract infection. No drug-related serious adverse events (SAEs) were reported. There were 3 discontinuations from study therapy: in 2 subjects, the adverse events were drug-related (ie, mild drowsiness and moderate nausea in 1 subject and moderate allergic reaction in 1 subject), and in 1 subject, the adverse event was not related to study drug (ie, an unrelated SAE of anaphylaxis due to nut allergy).

Although sulbactam is available as a standalone product in a small number of countries (eg, Combactam, Germany), the vast majority of human use is in combination with β -lactams (eg, Unasyn, combination ampicillin/sulbactam). The clinical safety of sulbactam has been established by nearly 30 years of experience with Unasyn. Based on the product label, Unasyn is generally safe and well tolerated. The dose of sulbactam that will be used in combination with ETX2514 is the top dose approved for human use (1 g q6h, maximum daily dose of 4 g).⁹ The most frequently reported adverse events reported with Unasyn are nausea, vomiting, diarrhea, pain at the injection site, and skin rash. Hepatic dysfunction, including hepatitis and cholestatic jaundice, has been associated with the use of sulbactam. Hepatic toxicity is usually reversible; however, deaths have been reported. Routine monitoring of liver function will be conducted at baseline and during and after administration of ETX2514SUL.

In the Phase 1 study, the general safety profile of ETX2514 was unchanged when ETX2514 was co-administered with sulbactam, with imipenem/cilastatin, and with sulbactam and imipenem/cilastatin.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the safety profile of ETX2514SUL versus placebo in patients with cUTI, including AP.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the efficacy of ETX2514SUL in patients with cUTI, including AP, in the microbiologically modified Intent-to-Treat (m-MITT) Population;
- To compare the clinical cure rate in the 2 treatment groups in the modified Intent-to-Treat (MITT), m-MITT, Clinical Evaluable (CE), and Microbiological Evaluable (ME) Populations at the Test-of-Cure (TOC) Visit; and
- To compare the microbiological eradication rate in the m-MITT and ME Populations at the TOC Visit.

2.3 Exploratory Objective

The exploratory objective of this study is to evaluate the efficacy of ETX2514SUL against cUTIs caused by *A. baumannii* and by pathogens susceptible to imipenem plus ETX2514SUL but resistant to imipenem in the m-MITT Population.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This study is a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of IV ETX2514SUL in patients with cUTIs who are otherwise relatively healthy. Patients providing informed consent and meeting all study eligibility criteria will be enrolled in the study and have a pre-treatment urine and blood sample obtained and submitted to the local laboratory. Approximately 80 patients will be randomized 2:1 to receive either 1 g ETX2514/1 g sulbactam IV or matching placebo q6h. All patients will receive background therapy with 500 mg IV imipenem/cilastatin q6h. Randomization will be stratified by baseline diagnosis (symptomatic cUTI versus AP). At least 30% of patients will have a diagnosis of AP at study entry.

Receipt of any long-acting, potentially-effective systemic antibiotic with activity against Gram-negative uropathogens for more than 24 hours within the 72-hour window prior to randomization is prohibited. However, patients who have received a single dose of a short-acting systemic antibiotic up to 24 hours prior to randomization may be randomized up to a maximum of 25% of the study enrollment. A short-acting antibiotic is defined as having a dosage frequency of more than once daily (eg, every 12 hours or more frequently). See Appendix C for a list allowed and disallowed antibiotics.

Any organism isolated from the blood or urine cultures will be identified by genus and species by the local laboratory. Urine organisms will be cultured and quantified at the local laboratory, and susceptibility of the organism(s) may be performed per local laboratory standards. All baseline urine organisms that grow $\geq 10^5$ colony-forming units (CFU)/mL and are not deemed to be a contaminant, as detailed in the Microbiology Procedures Manual, are to be sent from the local laboratory to the central laboratory. Potential pathogens that grow in both the urine and blood will also be sent to the central laboratory prior to randomization.

For post-baseline urine cultures, only those potential pathogens that grow at $\geq 10^3$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory.

All blood organism(s) cultured at the local laboratory from blood samples (whether at baseline or post-baseline) and not deemed to be a contaminant per the Microbiology Procedures Manual will be sent to the central laboratory for confirmation of identification and susceptibility testing.

Although local susceptibility testing is not a requirement, when local susceptibility testing indicates non-susceptibility to imipenem (eg, intermediate susceptibility or resistance to imipenem) but the patient is stable or clinically improving, the patient should remain on study drug at the discretion of the Investigator. Prior to discontinuation from study drug, the Investigator should discuss such cases with the Medical Monitor.

Day 1 is defined as the first day of study drug administration. The subsequent study days are defined by the number of calendar days thereafter. The duration of antibiotic treatment with study drug therapy will be 7 days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

All patients should receive at least 8 doses of IV study drug before the Investigator considers the patient to be a clinical failure and discontinues the patient from study drug therapy. No oral switch option is allowed. Patients who withdraw from study drug dosing should perform all End of

Treatment (EOT) Visit procedures and should be followed through the Late Follow-up (LFU) Visit for safety assessments, even if they withdraw from dosing due to clinical failure.

Throughout the study, all patients will be monitored for signs and symptoms of cUTI or AP and the occurrence of adverse events. Laboratory data, including chemistry panels, complete blood counts, and samples for urine and blood cultures, as well as electrocardiograms (ECGs), will be collected from all patients at specified times throughout the study.

Sparse PK sampling (ie, a total of 5 samples per patient) will be performed to refine the population PK model. To maintain the blind, PK samples will be collected from both treatment groups. Samples obtained from the ETX2514SUL group will be analyzed using a validated assay by a central bioanalytical laboratory.

Patients will be enrolled in the study for approximately 21 days, with a maximum duration of study participation of 30 days. Screening procedures can be performed as standard of care within 48 hours prior to randomization on Day 1, with the exception of local laboratory serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. The Treatment Period begins on Day 1, and study drug will be administered for 7 calendar days (or up to 14 days in patients with concurrent bacteremia). The EOT Visit will be completed on the final dosing day or the following day (allowing for a 1-day window to complete EOT procedures). The Test-of-Cure (TOC) Visit will be completed 7 days (± 1 day) after the EOT for all patients. The LFU Visit will be completed 7 days (± 2 days) after the TOC Visit for all patients.

3.2 Study Indication

The indication of this study is the treatment of cUTIs, including AP.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. A signed informed consent form (ICF). If a study patient is unable to provide informed consent due to their medical condition, the patient's legally authorized representative may consent on behalf of the study patient as permitted by local law and institutional Standard Operating Procedures;
2. Male or female, 18 to 90 years of age, inclusive;
3. Expectation, in the judgment of the Investigator, that the patient's cUTI would require initial hospitalization and treatment with IV antibiotics;
4. Documented or suspected cUTI or AP, as defined below:
 - o cUTI
 - Signs or symptoms evidenced by at least 2 of the following:
 - Documented fever accompanied by chills, rigors, or warmth;
 Note: fever must be observed and documented by a health care provider within 24 hours of Screening (oral, tympanic, rectal, or core temperature $>38^{\circ}\text{C}$ [$>100.4^{\circ}\text{F}$]).
 - Nausea or vomiting within 24 hours of Screening, as reported by the patient;
 - Dysuria, increased urinary frequency, or urinary urgency; or
 - Lower abdominal pain, pelvic pain, or suprapubic tenderness on physical examination;
 - *And* urine specimen with evidence of pyuria:
 - Positive leukocyte esterase on urinalysis; or
 - White blood cell count ≥ 10 cells/ mm^3 in unspun urine; or
 - White blood cell count ≥ 10 cells/high-power field (hpf) in urine sediment;
 - *And* at least 1 of the following associated risks:
 - Use of intermittent bladder catheterization or presence of an indwelling bladder catheter;
 Note: indwelling bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of the Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated.
 - Current known functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a post-void residual urine volume of ≥ 100 mL;

- Complete or partial obstructive uropathy (eg, nephrolithiasis, tumor, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT);
 - Azotemia, defined as blood urea nitrogen >20 mg/dL, blood urea >42.8 mg/dL, or serum creatinine >1.4 mg/dL, due to known prior intrinsic renal disease; or
 - Chronic urinary retention in men (eg, previously diagnosed benign prostatic hypertrophy);
- AP
- Signs or symptoms evidenced by at least 2 of the following:
 - Documented fever accompanied by chills, rigors, or warmth;
Note: fever must be observed and documented by a health care provider within 24 hours of Screening (oral, tympanic, rectal, or core temperature >38°C [$>100.4^{\circ}\text{F}$]);
 - Nausea or vomiting within 24 hours of Screening, as reported by the patient;
 - Dysuria, increased urinary frequency, or urinary urgency; or
 - Acute flank pain (onset within 7 days prior to randomization) or costo-vertebral angle tenderness on physical examination;
 - *And* urine specimen with evidence of pyuria:
 - Positive leukocyte esterase on urinalysis; or
 - White blood cell count ≥ 10 cells/mm³ in unspun urine; or
 - White blood cell count ≥ 10 cells/hpf in urine sediment;
5. Have a baseline urine culture specimen obtained within 48 hours prior to randomization;
Note: patients may be randomized into this study and start IV study drug therapy before the Investigator knows the results of the baseline urine culture.
6. Expectation, in the judgment of the Investigator, that any implanted urinary instrumentation (eg, nephrostomy tubes, ureteric stents) will be surgically removed or replaced before or within 24 hours after randomization, unless removal or replacement is considered unsafe or contraindicated;
Note: temporary bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated.
7. Expectation, in the judgment of the Investigator, that the patient will survive with effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study;
8. Women of childbearing potential (ie, not post-menopausal or surgically sterilized) must have a negative pregnancy test (serum or urine) before randomization. Participating women of childbearing potential must be willing to consistently use 2 highly effective methods of contraception (ie, condom plus spermicide, combined oral contraceptive, implant, injectable,

indwelling intrauterine device, or a vasectomized partner) from Screening until at least 30 days after administration of the last dose of study drug; and

9. Male participants will be required to use condoms with a spermicide during sexual intercourse between Screening and at least 90 days after administration of the last dose of study drug.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Presence of any known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy, including but not limited to the following:
 - Perinephric abscess;
 - Renal corticomedullary abscess;
 - Uncomplicated urinary tract infection (UTI);
 - Any recent history of trauma to the pelvis or urinary tract;
 - Polycystic kidney disease;
 - Chronic vesicoureteral reflux;
 - Previous or planned renal transplantation;
 - Patients receiving dialysis, including hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration;
 - Previous or planned cystectomy or ileal loop surgery; and
 - Known or suspected infection that is caused by a pathogen(s) that is known to be resistant to imipenem or BL/BLI combinations, including infection caused by fungi (eg, candiduria) or mycobacteria (eg, urogenital tuberculosis);
2. Presence of suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination;
3. Gross hematuria requiring intervention other than administration of study drug or removal or exchange of a urinary catheter;
4. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy prior to EOT);
5. Renal function at Screening as estimated by creatinine clearance <70 mL/min using the Cockcroft-Gault formula and serum creatinine value obtained from a local laboratory;
6. Known non-renal source of infection such as endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to randomization that would interfere with evaluation of response to the study antibiotics;

7. Any signs of severe sepsis, including but not limited to the following:
 - Shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline (if known) that is not responsive to fluid challenge; or
 - Disseminated intravascular coagulation as evidenced by prothrombin time or partial thromboplastin time $\geq 2 \times$ the upper limit of normal (ULN) or <50,000 platelets/mm³ at Screening in patients in whom severe sepsis is suspected;
8. Pregnant or breastfeeding women;
9. Known seizure disorder requiring current treatment with anti-seizure medication which, in the opinion of the Investigator, would prohibit the patient from complying with the protocol. Patients with a history of epilepsy or who are on stable treatment (ie, no change in therapy within 30 days) with well controlled seizure disorder (ie, no recurrent episodes in the past 30 days) may be considered for enrollment in the study;
10. Treatment within 30 days prior to randomization with any cancer chemotherapy, immunosuppressive medications for transplantation, or medications for rejection of transplantation;
11. Patient requires continuing treatment with probenecid, methotrexate, ganciclovir, valproic acid, or divalproex sodium during the study;
12. Evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy;
13. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>3 \times$ ULN or total bilirubin $>2 \times$ ULN at Screening;
14. Receipt of a single dose of a long-acting, potentially-effective systemic antibiotic with activity against Gram-negative uropathogens for more than 24 hours within the 72-hour window prior to randomization. However, patients may enroll who:
 - Have received >48 hours of prior antimicrobial therapy, and (1) in the opinion of the Investigator, have failed that preceding antimicrobial therapy (ie, have worsening signs and symptoms), and (2) are documented to have a cUTI or AP that is caused by a pathogen resistant to the prior therapy, and (3) the causative pathogen is known not to be resistant (eg, the causative pathogen is either susceptible, intermediate, or unknown susceptibility) to imipenem;
 - Develop signs and symptoms of cUTI or AP while taking a systemic antibiotic for another indication (other than ETX2514SUL or imipenem/cilastatin), including antimicrobial prophylaxis for recurrent UTI; or
 - Received a single dose of a short-acting (ie, having a dosage frequency of more than once daily [eg, every 12 hours or more frequently]) systemic antibiotic up to 24 hours prior to randomization. No more than 25% of patients will be enrolled who meet this criterion;
15. Requirement at time of randomization for any reason for additional systemic antimicrobial therapy (including antibacterial, antimycobacterial, or antifungal therapy) other than study drug, with the exception of a single oral dose of any antifungal treatment for vaginal candidiasis;

16. Likely to require the use of an antibiotic for cUTI or AP prophylaxis during the patient's participation in the study (from randomization through the LFU Visit);
17. Known history of human immunodeficiency virus infection and known recent CD4 count $<200/\text{mm}^3$ within the last year;
18. Presence of significant immunodeficiency or an immunocompromised condition, including hematologic malignancy, bone marrow transplant, or receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (equivalent to ≥ 20 mg/day of prednisone or systemic equivalent for ≥ 2 weeks);
19. Presence of neutropenia (absolute neutrophil count $<1000/\text{mm}^3$) obtained from a local laboratory at Screening;
20. Presence of thrombocytopenia (especially in patients diagnosed with disseminated intravascular coagulation or at risk of serious bleeding) $<50,000$ platelets/ mm^3 obtained from a local laboratory at Screening;
21. A QT interval corrected using Fridericia's formula (QTcF) >480 msec;
22. History of significant hypersensitivity or allergic reaction to any β -lactam, any contraindication to the use of imipenem/cilastatin based on local approved prescribing information (eg, Summary of Medicinal Product Characteristics), any contraindication to the excipients used in the respective formulations, or any contraindication to the use of β -lactam antibiotics;
23. Participation in a clinical study involving investigational medication or an investigational device within the last 30 days or 5 half-lives, whichever is longer, prior to randomization;
24. Unable or unwilling, in the opinion of the Investigator, to comply with the protocol; or
25. Any patients previously randomized in this study.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

For patients in whom the creatinine clearance drops below 70 mL/min after baseline, the Investigator should repeat serum creatinine at the local laboratory once they receive the abnormal laboratory result to confirm the value. The Investigator may withdraw the patient from the study when a dose adjustment for imipenem is necessary or when patient safety is at risk. However, if the Investigator believes that the creatinine clearance decrease is not clinically significant or will quickly reverse, the Medical Monitor will be contacted to discuss if the patient may continue in the study or should be withdrawn.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the EOT Visit, and the patient should be followed through the LFU Visit. If a patient withdraws after the EOT Visit, study staff should make every effort to complete the full panel of assessments scheduled for the study visit following the date of withdrawal (TOC Visit or LFU Visit), as applicable. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

In the case of patients lost to follow-up, attempts to contact the subject must be made and documented in the patient's medical records.

Withdrawn subjects will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Study drug will be administered IV in a double-blind design. The study will be constructed with 2 treatment arms (2:1) as follows:

- 1 g ETX2514/1g sulbactam IV administered q6h over 3 hours, or
- Matching placebo IV administered q6h over 3 hours.

In addition, all patients will be administered background therapy with 500 mg IV imipenem/cilastatin q6h infused over 30 minutes. Infusions of study drug will occur q6h for 7 calendar days, with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

5.2 Rationale for Dosing

The doses of ETX2514 and sulbactam to be evaluated in this study have been selected based on PK data generated in nonclinical experiments and a Phase 1 PK study that evaluated SAD and MAD of ETX2514, evaluation of safety in Good Laboratory Practice toxicology studies, and PK/PD. Data from these studies are provided in more detail in the Investigator's Brochure.

ETX2514 1 g was generally well tolerated in multiple doses in the Phase 1 study. Sulbactam 1 g was generally well tolerated as a single dose in the Phase 1 study. The total daily dose of sulbactam being used in the current study is consistent with the US Product Circular for Unasyn, in which the maximum approved daily dose for sulbactam is 4 g, which is equivalent to 1 g sulbactam q6h.

The ETX2514SUL regimen of 1 g ETX2514/1 g sulbactam infused over 3 hours q6h is consistent with the PK/PD targets established for a susceptibility breakpoint against *A. baumannii* of 4 mg/L.

5.3 Randomization and Blinding

Qualifying patients will be randomized in a 2:1 ratio to receive 1 g ETX2514/1 g sulbactam or placebo via the Interactive Response Technology (IRT) system. All patients will receive 500 mg IV imipenem/cilastatin q6h.

Randomization will be stratified by baseline diagnosis (symptomatic cUTI versus AP). A manual will be provided that describes the IRT system and includes user instructions.

At least 30% of patients will have a diagnosis of AP at study entry.

Patients who have received a single dose of short-acting antibiotic (see Appendix C for a list of allowed and disallowed antibiotics) for cUTI or AP within 24 hours of randomization will comprise a maximum of approximately 25% of the study enrollment. Patients who have received any potentially therapeutic and long-acting antibiotic for more than 24 hours within the 72-hour window of the start of administration of the first dose of study drug will be excluded from the study.

A randomization notification will be sent to the unblinded pharmacist (or appropriately qualified unblinded designee) at the site. A blinded randomization notification will be sent to the appropriate blinded site personnel.

The Investigator, site personnel, Sponsor, and the Sponsor’s designees involved in monitoring, data management, and other aspects of the study will be blinded to treatment assignment. An unblinded site monitor will be assigned to review unblinded pharmacy data and will follow documented procedures to ensure that the blind is maintained throughout the study.

5.4 Breaking the Blind

The Sponsor designee (eg, IRT vendor, etc.) will have a designated randomization administrator who will maintain the randomization codes in accordance with Standard Operating Procedures to ensure that the blind is properly maintained and that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes or SAE reporting).

Unblinding should only occur in the event of an emergency or adverse event for which it is necessary to know the study drug treatment to determine an appropriate course of therapy. If the patient’s study drug must be unblinded, the Investigator or qualified designee should contact IRT, but not the site’s unblinded pharmacist, for the study drug information. The IRT documentation indicating the blind break must be retained with the patient’s source documentation in a way as to not unblind the treatment assignment to other site or Sponsor personnel.

If possible, the Investigator should attempt to contact the site monitor or the Medical Monitor prior to unblinding in order to get additional information about the study drug. If not possible, the Investigator should notify the site monitor or Medical Monitor as soon as possible of the unblinding without disclosing the treatment assignment of the unblinded patient. The Investigator must document the patient’s identification, reason for breaking the blind, and the date and time for breaking the blind.

After the database is locked and the Statistical Analysis Plan (SAP) is final, the study blind codes will be broken.

5.5 Prior and Concomitant Medications and/or Procedures

5.5.1 Excluded Medications and/or Procedures

Treatment with any of the following concomitant medications or procedures is prohibited:

[REDACTED]

- Methotrexate;
- Ganciclovir;
- Valproic acid or divalproex sodium;
- Any cancer chemotherapy, immunosuppressive medications for transplantation, or medication for rejection of transplantation;
- Any additional or adjunctive non-study-specific antibiotic therapy administered with the intention of treating cUTI, AP, or other infection. Agents with Gram-positive only coverage (eg, vancomycin, daptomycin, or linezolid) for suspected or identified Gram-positive organisms may be considered, as deemed necessary by the Investigator;

- Any antifungal therapy other than topical antifungal or a single oral dose of any antifungal treatment for vaginal candidiasis; or
- Bladder irrigations with any antiseptic or antibiotic.

5.5.2 Restricted Medications and/or Procedures

Treatment with any of the following concomitant medications or procedures is restricted:

- Antibiotics for the treatment of *Clostridium difficile* (eg, fidaxomicin), or
- Topical antibiotics other than those used for bladder irrigation.

5.5.3 Documentation of Prior and Concomitant Medication Use

Reasonable effort will be made to determine all relevant treatments (including all antibiotics, prescription and non-prescription medications, herbal medications and vitamin supplements, supportive therapies, and non-pharmacologic treatments) received within 14 days before the first dose of study drug and during the study. The name, route of administration, dose, frequency, indication, and duration of the treatment will be recorded in the eCRF. The date and time of start and stop of any antibiotic therapy received within 14 days before the first dose of study drug and during the study will also be recorded.

Patients cannot participate in any other investigational medication trial while participating in this study, or have taken any investigational product within 30 days prior to the first dose of study drug in this study.

5.6 Drug Supplies

5.6.1 Formulation and Packaging

██
██
██
██

Study drugs will be labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines.

5.6.2 Study Drug Preparation and Dispensing

An unblinded pharmacist (or qualified designee) will prepare the study drug according to the requirements outlined in the Pharmacy Manual. The IV bags will be labeled with the date and time of study drug preparation and patient identification number using the study supplied labels and will be transferred to the blinded study staff for administration to the patient. Reconstituted study drug should be administered according to the requirements outlined in the Pharmacy Manual.

5.6.3 Study Drug Administration

The unblinded pharmacist (or qualified designee) will be responsible for providing blinded study personnel with study drug ready for IV infusion. Patients will receive treatment in accordance with the blinded randomization schedule administered via an IRT system. Patients will receive randomized treatment administered as described in the Pharmacy Manual.

Patients will receive all infusions by drip infusion or programmable infusion pump while seated or partially reclined in bed. The times at which each infusion is started and stopped must be recorded. If a dose is interrupted for more than 10 minutes, the interruption and reason for interruption should be noted in the source documents. Any missed dose should also be noted in the source documents with the reason for the missed dose. Study drug infusions will be administered q6h (± 15 minutes). Infusions that fall outside of the q6h (± 15 minutes) dosing schedule will be considered protocol deviations. It is critical that administration and infusion time be captured in the eCRF based on actual time. Windows for administration and infusion provided should be used sparingly, and the patient should remain on schedule based on the q6h administration requirement.

Dosing time is relative to the start of infusion. For additional information on study drug product dilution, infusion volumes, and dispensing instructions, refer to the Pharmacy Manual.

5.6.4 Treatment Compliance

The infusion date and start and stop times will be recorded in the source documents and eCRF. Treatment compliance will be calculated based on the number of doses received and expected as detailed in the SAP.

5.6.5 Storage and Accountability

The unblinded pharmacist or designated unblinded study personnel will ensure that all study drugs are stored in a locked, secure area with limited access. Study drugs will be stored under recommended storage conditions per the label and in accordance with the Pharmacy Manual.

The date and time of preparation of study drug will be recorded on the IV bags. Refer to the Pharmacy Manual for additional information.

The Investigator is responsible for maintaining a current record of inventory/drug accountability. Vials may not be discarded until inventory and drug accountability is performed by the unblinded monitor.

6 STUDY PROCEDURES

A detailed schedule of procedures is provided in Appendix A.

6.1 Informed Consent

Informed consent must be obtained before any study procedures are performed. The ICF will be signed at Screening. As permitted by local law and institutional Standard Operating Procedures, in cases of a lack of decision-making capacity, informed consent on behalf of the patient may be provided by a legally authorized representative.

6.2 Screening (-48 hours to Day 1)

Screening can occur up to 48 hours before the first dose of study drug. All Screening procedures must be performed prior to randomization and the first dose of study drug. Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug.

The following procedures will be performed at Screening:

- Obtain informed consent;
- Review all inclusion and exclusion criteria;
- Obtain medical/surgical history, including urological history; record inactive conditions diagnosed within the previous 5 years, complete urological/renal history, and all active conditions;
- Record prior and concomitant medications;
- Obtain demographics, including sex, age, race, and ethnicity;
- Perform a complete physical examination, including height and weight;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Perform pregnancy test for women of childbearing potential only;
- Collect blood samples for serum chemistry, hematology, and blood cultures;
- Collect urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for urinalysis and urine cultures;
- Perform 12-lead ECG and consult the study Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF >480 msec); and
- Assess adverse events.

6.3 Treatment Period – Day 1 to Day 14

All patients will receive randomized IV treatment q6h for 7 days (28 doses) or up to 14 days in patients with concurrent bacteremia.

6.3.1 Day 1

The following procedures will be performed at Day 1:

- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Collect PK sample, pre-dose;
- Administer imipenem/cilastatin;
- Collect pre-dose blood samples for:
 - Serum chemistry; and
 - Hematology;
- Collect pre-dose urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for:
 - Urinalysis for all patients; and
 - Urine cultures for any patient who has received a single dose of a short-acting antibiotic in the 24 hours prior to randomization, or for patients who failed preceding antimicrobial therapy;

Note: this sample should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible).

- Randomize patient to study drug via IRT;
- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.3.2 Day 2

The following procedures will be performed at Day 2:

- Record concomitant medications;
- Perform a limited physical examination;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Collect blood sample for blood cultures, if applicable;
- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.3.3 Day 3

The following procedures will be performed at Day 3:

- Record concomitant medications;
- Perform a complete physical examination, including weight;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Collect blood sample for:
 - Serum chemistry;
 - Hematology; and
 - Blood cultures, if applicable;
- Collect urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for urinalysis;
- If PK samples will not be collected on Day 4, collect post-dose PK samples at the end of the infusion when the infusion pump is turned off, 0.5 hours after the end of the infusion, 2 hours after the end of the infusion, and 3 hours after the end of infusion (prior to the start of the next infusion);

Note: when possible, PK samples should be collected on Day 4. If not possible on Day 4, post-dose PK samples may be collected on Day 3 or Day 5 instead of Day 4, at the discretion of the Investigator.

- If PK samples are collected, perform 12-lead ECG as close as possible to the end of the infusion of study drug administration associated with the PK samples;
- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.3.4 Day 4

The following procedures will be performed at Day 4:

- Record concomitant medications;
- Perform a limited physical examination;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Collect blood sample for blood cultures, if applicable;
- If PK samples were not collected on Day 3, collect post-dose PK samples at the end of the infusion when the infusion pump is turned off, 0.5 hours after the end of the infusion, 2 hours

after the end of the infusion, and 3 hours after the end of infusion (prior to the start of the next infusion);

Note: when possible, PK samples should be collected on Day 4. If not possible on Day 4, post-dose PK samples may be collected on Day 3 or Day 5 instead of Day 4, at the discretion of the Investigator.

- If PK samples are collected, perform 12-lead ECG as close as possible to the end of the infusion of study drug administration associated with the PK samples;
- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.3.5 Day 5

The following procedures will be performed at Day 5:

- Record concomitant medications;
- Perform a complete physical examination, including weight;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Assess clinical outcome;
- Collect blood sample for:
 - Serum chemistry;
 - Hematology; and
 - Blood cultures, if applicable;
- Collect urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for urine cultures;
- If post-dose PK samples were not collected on either Day 3 or Day 4, collect post-dose PK samples at the end of the infusion when the infusion pump is turned off, 0.5 hours after the end of the infusion, 2 hours after the end of the infusion, and 3 hours after the end of infusion (prior to the start of the next infusion);

Note: when possible, PK samples should be collected on Day 4. If not possible on Day 4, post-dose PK samples may be collected on Day 3 or Day 5 instead of Day 4, at the discretion of the Investigator.

- If PK samples are collected, perform 12-lead ECG as close as possible to end of the infusion of study drug administration associated with the PK samples;
- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.3.6 Day 6

The following procedures will be performed at Day 6:

- Record concomitant medications;
- Perform a limited physical examination;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Collect blood sample for blood cultures, if applicable;
- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.3.7 Day 7 to Day 14/End of Treatment Visit

Patients will be treated for 7 days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia. If EOT occurs on Day 7, Day 7 study procedures may be considered the EOT Visit study procedures. Day 7 to Day 14 study procedures are only required if the patient receives IV study treatment on Day 7 to Day 14. If EOT has already occurred, study procedures are not required to be performed. The EOT Visit will be completed on the final dosing day or the following day (allowing for a 1-day window to complete EOT procedures).

The following procedures will be performed at Day 7 to Day 14 and at the EOT Visit:

- Record concomitant medications;
- Perform a complete physical examination, including weight (Day 7 and EOT Visit only);
- Perform a limited physical examination (Day 8 to Day 14 only);
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Assess clinical outcome (Day 7 and EOT Visit only);
- Perform pregnancy test for women of childbearing potential only (EOT Visit only);
- Collect blood sample for:
 - Serum chemistry (Day 7 and EOT Visit only);
 - Hematology (Day 7 and EOT Visit only); and
 - Blood cultures, if applicable;
- Collect urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for:
 - Urinalysis (Day 7 and EOT Visit only); and
 - Urine cultures;

- Administer imipenem/cilastatin;
- Administer study drug; and
- Assess adverse events.

6.4 Test-of-Cure Visit

The TOC Visit will occur 7 days (± 1 day) after the EOT Visit.

The following procedures will be performed at the TOC Visit:

- Record concomitant medications;
- Perform a limited physical examination;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;
- Assess clinical outcome;

Note: if a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC and LFU Visits, and the assessment of clinical response by the Investigator should be listed as “failure at EOT.”

- Collect blood samples for:
 - Serum chemistry;
 - Hematology; and
 - Blood cultures, if applicable;
- Collect urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for:
 - Urinalysis; and
 - Urine cultures; and
- Assess adverse events.

6.5 Late Follow-up Visit

The LFU Visit will occur 7 days (± 2 days) following the TOC Visit. The LFU Visit should be performed as an in-office visit; however, if the patient is unable to attend the LFU Visit at the site, the patient may be contacted by telephone call for follow-up assessment of concomitant medications, clinical signs and symptoms, and adverse events.

The following procedures will be performed at the LFU Visit:

- Record concomitant medications;
- Perform a limited physical examination;
- Obtain vital signs, including blood pressure, heart rate, and respiratory rate;
- Assess clinical signs and symptoms;

- Assess clinical outcome;
 - Note: if a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC Visit and LFU Visit, and the assessment of clinical response by the Investigator should be listed as “failure at EOT or TOC.”
- Collect blood samples for:
 - Serum chemistry;
 - Hematology; and
 - Blood cultures, if applicable;
- Collect urine sample by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination for:
 - Urinalysis; and
 - Urine cultures; and
- Assess adverse events.

6.6 Withdrawal Procedures

For patients who are withdrawn from the study prior to completion of study drug, complete an EOT Visit at the time of study termination. For patients who are withdrawn from the study after the EOT Visit but prior to completion of the study, complete the next scheduled visit (either TOC or LFU Visit) at the time of study termination.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Parameter

The primary efficacy parameter is the proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the TOC Visit.

7.2 Secondary Efficacy Parameters

The secondary efficacy parameters include the following:

- Proportion of patients with a response of clinical cure in the Modified Intent-to-Treat (MITT), m-MITT, Clinical Evaluable (CE), and Microbiologic Evaluable (ME) Populations at the TOC Visit; and
- Proportion of patients with a response of microbiologic eradication in the m-MITT and ME Populations at the TOC Visit.

7.3 Other Efficacy Parameters

The exploratory efficacy parameters include the following:

- Proportion of patients with a response of sustained microbiologic eradication in the m-MITT and ME Populations at the LFU Visit;
- Proportion of patients with a response of sustained clinical cure in the MITT, m-MITT, CE, and ME Populations at the LFU Visit;
- Proportion of patients with a response of clinical cure in the MITT and m-MITT Populations at Day 5;
- All-cause mortality through the LFU Visit in the MITT Population;
- Summary (number and percentage of patients) of the assessment of clinical signs and symptoms of cUTI and AP at each time point throughout the study by treatment group in the MITT Population; and
- Descriptive statistics of the length of hospital stay by treatment group for the MITT Population.

7.4 Overall Response

The primary efficacy outcome is a composite outcome (overall response) and is programmatically determined based on the clinical and microbiologic outcomes (see Sections 7.6 and 7.8, respectively) as 1 of the following overall responses:

Overall success: a patient who is deemed a clinical cure AND who achieved microbiologic eradication.

Overall failure: a patient who is deemed a clinical failure OR is deemed to have microbiological persistence.

Overall indeterminate: insufficient data are available to determine if the patient is an overall success or failure.

7.5 Assessment of Clinical Signs and Symptoms

Clinical signs and symptoms will be assessed at Screening, daily during IV treatment beginning on Day 2, at the EOT Visit, at the TOC Visit, and at the LFU Visit. When possible, the same study personnel should complete the assessments at approximately the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method and will be recorded in the appropriate eCRF. The same method of measuring a patient's body temperature should be used throughout the study.

The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe:

- Urinary frequency,
- Urinary urgency,
- Dysuria,
- Nausea,
- Vomiting,
- Abdominal pain,
- Suprapubic pain or discomfort,
- Flank pain, and
- Costo-vertebral angle tenderness.

7.6 Clinical Outcome

Based on the assessment of signs and symptoms, the Investigator will choose 1 of the following clinical outcomes at the Day 5, EOT, and TOC Visits:

Clinical cure: complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted.

Clinical failure: symptoms of cUTI or AP present at study entry have not significantly improved or completely resolved, or new symptoms of cUTI or AP have developed and require the initiation of a non-study antibacterial drug therapy, or death.

Clinical indeterminate: insufficient data are available to determine if the patient is a cure or failure.

Based on the assessment of signs and symptoms, the Investigator will choose 1 of the following clinical outcomes at the LFU Visit:

Sustained clinical cure: met criteria for clinical cure at the TOC Visit and the LFU Visit.

Relapse: clinical cure at the TOC Visit but signs and symptoms of cUTI or AP are present at the LFU Visit.

Clinical failure: clinical failure at the TOC Visit carried forward to the LFU Visit or death between the TOC Visit and LFU Visit.

Clinical indeterminate: insufficient data are available to determine if the patient is a sustained clinical cure or clinical relapse.

Note: if a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC and LFU Visits, and an assessment of clinical response by the Investigator will be listed as “failure at EOT.”

7.7 Microbiologic Assessments

Urine culture samples will be obtained at Screening or Day 1, Day 5, Day 7, the EOT Visit, the TOC Visit, the LFU Visit, and any time the patient is deemed to have failed while on therapy. In patients with concurrent bacteremia who receive blinded study drug on Day 8 to Day 14, urine culture samples will be obtained daily. Urine cultures will be performed by the local laboratory. Additionally, a urinalysis including urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH will be performed at Screening, Day 1, Day 3, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit. Screening urinalysis will be performed by the local laboratory; all other urinalysis samples will be sent to the central laboratory.

A urine sample taken to support diagnosis or to treat a medical condition within 48 hours prior to the first dose of study drug can be used for baseline microbiologic assessments if the organism(s) cultured were obtained and stored for shipment to the designated central laboratory. Otherwise, a repeat urine sample for baseline microbiologic assessments is required.

A repeat urine sample for culture must be obtained prior to the start of study drug treatment for any patient enrolled in the study who has received a single dose of a short-acting antibiotic in the 24 hours prior to randomization or for patients who failed preceding antimicrobial therapy. This sample should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible).

Urine culture samples must be obtained through 1 of the following methods that minimizes the risk of bacterial contamination:

- Clean-catch mid-stream,
- Newly-inserted Foley catheter (bag specimens are not permitted),
- Bladder needle aspiration, or
- Ureter aspiration.

Baseline urine cultures must grow 1 or 2 bacterial organisms, each at $\geq 10^5$ CFU/mL. If a patient grows ≥ 3 organisms in the urine, the urine culture will be considered contaminated unless ≥ 1 of the organisms also grows in a concurrently obtained blood culture.

Two sets of blood culture samples must be obtained from 2 separate venipuncture sites at Screening. Each set is collected from a separate venipuncture and consists of 1 aerobic and 1 anaerobic blood culture bottle. Each set of blood cultures should be collected by direct venipuncture from independent sites approximately 15 to 30 minutes apart. If baseline blood cultures are positive and not considered contaminated, repeat blood cultures should be obtained daily until negative or if the patient is a treatment failure. To avoid unnecessary blood draws, the

Investigator may wait until the result of the prior blood culture is known before performing the next blood culture.

The local laboratory will culture each sample for organism identification, quantification (urine only), and susceptibility testing. Any organism isolated from the blood or urine will be identified by genus and species by the local laboratory. Potential pathogen(s) cultured at the local laboratory from urine or blood samples will be sent to a designated central laboratory for confirmation of identification and susceptibility testing results.

Only those baseline potential pathogens that grow in the urine at $\geq 10^5$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory. Potential pathogens that grow in both the urine and blood will also be sent to the central laboratory prior to randomization.

For post-baseline urine cultures, only those potential pathogens that grow at $\geq 10^3$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory.

Although local susceptibility testing is not a requirement, when local susceptibility testing indicates non-susceptibility to imipenem (eg, intermediate susceptibility or resistance to imipenem) but the patient is stable or clinically improving, the patient should remain on study drug at the discretion of the Investigator. Prior to discontinuation from study drug, the Investigator should discuss such cases with the Medical Monitor.

When a patient's urine culture grows only Gram-positive organisms, but the patient is clinically improving, the patient may remain on study drug without additional Gram-positive antibiotic coverage at the Investigator's discretion. Patients who are not clinically improving should be discontinued from study drug at the discretion of the Investigator but should remain in the study to complete all study assessments.

7.8 Microbiologic Outcome

Per-patient microbiological response is determined programmatically based on the results of blood and urine cultures as 1 of the following outcomes at the Day 5, EOT, and TOC Visits:

Microbiologic eradication: the demonstration that the baseline bacterial pathogen(s) is reduced to $< 10^4$ CFU/mL according to the Food and Drug Administration (FDA) criteria and $< 10^3$ CFU/mL according to the European Medicines Agency (EMA) criteria on urine culture and negative on repeat blood culture (if positive at baseline).

Microbiologic persistence: the urine culture grows $\geq 10^4$ CFU/mL for the FDA ($\geq 10^3$ CFU/mL for the EMA) of any of the baseline pathogen(s) identified at study entry and/or a blood culture demonstrates the same baseline pathogen(s). Patients who are a persistence at EOT will be considered a persistence at TOC.

Microbiologic indeterminate: no follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated. For a baseline blood pathogen, no follow-up blood culture is available.

Per-patient microbiological response is determined programmatically based on the results of blood and urine cultures as 1 of the following outcomes at the LFU Visit:

Sustained microbiologic eradication: microbiologic eradication at the TOC Visit and the LFU Visit.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. Beginning at Screening, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (ie, the relationship cannot be ruled out).

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. The reference safety information for ETX2514SUL is included in the Investigator's Brochure currently in force. The reference

safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
 - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
 - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug-
 - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
 - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-
 - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
 - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
 - NOTE: an adverse event or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
 - NOTE: any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
 - NOTE: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting – Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to ██████████ Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, ██████████ Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to ██████████ Safety at ██████████ or call the ██████████ SAE hotline (phone number listed below), and fax the completed paper SAE form to ██████████ (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: ██████████ Clinical Safety

██████████ SAE hotline – US:

Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3

Fax: +1-866-336-5320 or +1-513-579-0444

E-mail: ██████████

██████████ SAE hotline – Rest of World:

Telephone: +49 89 89 55 718 44

Fax: +49 89 89 55 718 104

E-mail: ██████████

Follow-up reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to ██████████ Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If the patient or partner of a subject participating in the study becomes pregnant during the study or within 120 days of discontinuing study drug, the Investigator should report the pregnancy to ██████████ Clinical Safety within 24 hours of being notified. ██████████ Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify [REDACTED] Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all investigators as required.

Expedited reporting of suspected unexpected serious adverse reactions related to imipenem/cilastatin (and any other non-investigational medical products) will not be necessary. Listings of cases related to imipenem/cilastatin will be included in the Development Safety Update Report.

8.6 Clinical Laboratory Evaluations

Standard clinical laboratory profiles for chemistry will be evaluated at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit. All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. All other samples are to be sent to the central laboratory. The Day 5 safety chemistry panel will be performed at the local laboratory and sent to the central laboratory.

Standard clinical laboratory profiles for hematology will be performed at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit.

A urinalysis including urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH will be performed at Screening, Day 1, Day 3, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit.

A highly sensitive urine or serum pregnancy test will be performed at Screening and at EOT on women of childbearing potential.

See Appendix B for a list of clinical laboratory analytes.

Standard of care safety laboratory profiles should also be performed by the local laboratory.

8.7 Vital Signs

Vital signs (including systolic and diastolic blood pressure, heart rate, and respiratory rate) will be taken after at least 5 minutes in a seated position. Vital signs will be recorded at Screening, all days that the patient receives study drug treatment, the EOT Visit, the TOC Visit, and the LFU Visit. Vital signs should be collected at the same time as assessments of signs and symptoms.

8.8 Electrocardiograms

Twelve-lead ECGs will be performed at baseline at Screening and repeated as close as possible to the end of the infusion of study drug administration on the day on which the post-dose PK samples are drawn (Day 3, Day 4, or Day 5; day selected at the discretion of the Investigator). All 12-lead ECGs will be performed after the patient has been in a supine position for at least 10 minutes. The value at Screening will be used for assessing the QTcF exclusion criterion. All 12-lead ECGs will be performed and read locally. The following ECG parameters will be recorded:

- Heart rate,
- QRS interval,
- PR interval,
- RR interval,
- QT interval, and
- QTc interval.

All ECGs will be evaluated for the presence of abnormalities by a qualified local physician. The ECGs will be classified as one of the following:

- Normal,
- Having a not clinically significant abnormality, or
- Having a clinically significant abnormality.

An example of a clinically significant abnormality may be a corrected QTcF >480 msec.

8.9 Physical Examinations

A complete physical examination will be performed at Screening, Day 3, Day 5, Day 7, and the EOT Visit. A limited physical examination will be performed at Day 2, Day 4, Day 6, Day 8 to Day 14 (if EOT has not already occurred), the TOC Visit, and the LFU Visit.

A complete physical examination must include source documentation of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral angle tenderness, and neuromuscular assessments. Weight will be obtained at all complete physical examinations; height will only be collected at Screening. Limited physical examinations are symptom based and do not include weight. When clinically indicated, a prostate exam can be performed, at the discretion of the Investigator.

Physical examinations may be performed at unscheduled time points if deemed necessary by the Investigator.

8.10 Safety Monitoring and Assessment of Abnormal Liver Function Tests

Management and discontinuation criteria for abnormal liver function tests (LFTs) have been designed to ensure patient safety and evaluate liver event etiology.¹⁰ Safety monitoring for LFTs will occur from randomization until 30 days following the last administration of study drug; however, any abnormal LFT will be monitored until the below criteria are met. Investigators should evaluate standard of care laboratory reports in addition to study laboratory reports when monitoring for LFTs.

Abnormal liver chemistry criteria:

The Investigator or sub-Investigator must review patient laboratory reports to identify if they meet the following criteria:

- Moderate abnormality:
 - AST or ALT $>3 \times$ ULN, or
 - Total bilirubin $>2 \times$ ULN.
- Severe abnormality:
 - AST or ALT $>3 \times$ ULN and total bilirubin $>2 \times$ ULN.

Action to be taken by Investigator:

If any 1 of the abnormal liver chemistry criteria is met, the Investigator or sub-Investigator must do the following:

- Obtain a detailed history of symptoms and prior or concurrent diseases. The Investigator should ensure that the medical history form captures any pre-existing illness that may be relevant in assessing hepatic function;
- Obtain a history of concomitant drug use (including over-the-counter/herbal/dietary supplements);
- Obtain a history of exposure to environmental chemical agents;
- Following the initial observed elevation, every effort should be made to have the patient reassessed within 48 hours to 72 hours. Repeat LFTs will be performed and sent to the central laboratory. Liver function tests may also be repeated via the local laboratory at the discretion of the Investigator;
- Patients who have an Investigator-assessed, study drug-related elevation of their LFTs must be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, alkaline phosphatase, and total bilirubin) completely return to normal range or return to the baseline level and associated clinical signs and symptoms return to baseline levels. If the elevation of LFTs is attributed to a non-study drug-related issue (eg, chronic hepatitis, chronic cholestasis, concomitant treatments, cardiovascular causes, etc.), the patient should be monitored until the LFTs stabilize or return to the patient's baseline level and associated clinical signs and symptoms return to baseline levels. The Investigator should contact the Medical Monitor to discuss additional management and follow-up of patients with elevation of LFTs;
- The event must be reported to [REDACTED] within 48 hours to 72 hours after its occurrence on a Liver Event Form;

- Consider a consultation with a specialist such as a hepatologist; and
- Consider performing liver imaging (ie, ultrasound, magnetic resonance imaging, computerized tomography).

Hy's Law definition:

The definition of Hy's Law is as follows:

1. Aspartate aminotransferase or ALT $>3 \times$ ULN,
2. Total bilirubin $>2 \times$ ULN, and
3. No evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's Syndrome.

If the first 2 criteria of Hy's Law are met, the case must be reported as an SAE.

Criteria for study drug discontinuation (severe hepatic abnormalities):

In the absence of an explanation for increased liver enzymes, the patient should be discontinued from the study drug. Discontinuation should be considered if:

- ALT or AST $>8 \times$ ULN;
- ALT or AST $>5 \times$ ULN for more than 2 weeks;
- AST or ALT $>3 \times$ ULN and total bilirubin $>2 \times$ ULN or international normalized ratio >1.5 ;
- AST or ALT $>3 \times$ ULN with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia [$>5\%$]); or
- Close monitoring for a patient with moderate hepatic laboratory test abnormality is not possible.

Follow-up examination:

If any abnormal liver chemistry criteria are met, the following assessments should be obtained at the LFU Visit and documented in a Liver Event Form:

- Clinical symptoms course;
- Concomitant medications: over-the-counter/herbal/dietary supplements (start and stop dates);
- Alcohol use;
- Risk factors for non-alcoholic steatohepatitis, such as diabetes, obesity, and hypertriglyceridemia;
- Autoimmune hepatitis/cholangitis;
- Wilson's disease; and

- Laboratory Assessments. Based on the patient's history, other testing may be appropriate, including:
 - Acute viral hepatitis (A, B, C, D, E or other infectious agents); and
 - Other laboratory tests, including international normalized ratio and direct bilirubin.

9 STATISTICS

9.1 Analysis Populations

The Intent-to-Treat (ITT) Population will include all patients randomized to study drug treatment (ETX2514SUL or placebo) regardless of whether the patient actually receives study drug.

The MITT Population will include patients who meet ITT criteria and receive any amount of study drug.

The m-MITT Population will include patients who meet MITT criteria and have at least 1 baseline uropathogen from an appropriately collected pre-treatment baseline urine or blood sample. To be considered a pathogen, the baseline urine culture must grow 1 or 2 bacteria isolates, each at $\geq 10^5$ CFU/mL. If ≥ 3 bacterial isolates are identified, the culture will be considered contaminated regardless of colony count unless 1 of the isolates, even if the CFU/mL is $< 10^5$, that grows in the urine is also isolated from a blood culture obtained within 48 hours before the start of administration of the first dose of study drug. If the same pathogen is present in both blood and urine cultures, even if the CFU/mL is $< 10^5$ in the urine, the organism will be considered a pathogen.

The CE Population will include patients who meet the MITT criteria and meet evaluability criteria (meet key inclusion criteria, do not have key exclusion criteria, received a minimum of at least 12 doses of IV treatment to be a clinical cure [at least 8 doses of IV treatment to be a clinical failure], received $\geq 80\%$ of anticipated doses, did not have a clinical response of indeterminate at the TOC visit).

The ME Population will include patients who meet m-MITT criteria and CE criteria and have an appropriately collected urine culture specimen and interpretable urine culture result at the TOC Visit.

The Primary Efficacy Population is the m-MITT Population.

The Safety Population will include patients who meet ITT criteria and receive any amount of study drug. All safety analyses will be based on actual treatment received.

The PK Population will include patients who meet MITT criteria and have at least 1 plasma PK sample drawn.

9.2 Statistical Methods

The efficacy analyses will be descriptive summaries. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for ETX2514SUL versus placebo. Listings of individual patient data will be produced. A complete analysis of efficacy and safety data will be performed and detailed in the SAP.

9.2.1 Patient Population and Characteristics

Enrollment, protocol deviations, and discontinuations from the study drug and the study will be summarized by treatment group. Demographics (age, race, ethnicity, and sex), medical and surgical history, baseline assessment of the clinical signs and symptoms, microbiological assessment, and study drug administration will also be summarized.

9.2.2 Analysis of Efficacy

For all efficacy analyses, patient data will be analyzed in the group to which the patient was randomized.

9.2.2.1 Primary efficacy analysis

The primary efficacy endpoint for this study is the proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the TOC Visit.

Patients will be programmatically categorized as a success, failure, or indeterminate response. Patients with missing data or who are lost to follow-up are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of overall success rate. Thus, patients with an indeterminate outcome are considered failures for the primary analysis. The number and percentage of patients in each treatment group with an overall success, failure, and indeterminate response will be determined. A 2-sided 95% confidence interval (CI) for the observed difference in the overall success rates (EXT2514SUL group minus placebo group [background imipenem/cilastatin therapy]) will be calculated using a continuity-corrected Z-statistic.

9.2.2.2 Secondary efficacy analysis

The secondary efficacy parameters include the following:

- Proportion of patients with a response of clinical cure in the MITT, m-MITT, CE, and ME Populations at the TOC Visit; and
- Proportion of patients with a response of microbiologic eradication in the m-MITT and ME Populations at the TOC Visit.

The number and percentage of patients in each response category for each of the secondary efficacy outcomes will be provided. Two-sided 95% CIs for the difference in outcome rates between the ETX2514SUL group and the placebo group (background imipenem/cilastatin therapy) will be provided.

9.2.2.3 Other efficacy analysis

Analyses of the other efficacy endpoints will be conducted in a similar manner as the analyses above for the following additional efficacy endpoints:

- Proportion of patients with a response of sustained microbiologic eradication in the m-MITT and ME Populations at the LFU Visit;
- Proportion of patients with a response of sustained clinical cure in the MITT, m-MITT, CE, and ME Populations at the LFU Visit;
- All-cause mortality through the LFU Visit in the MITT Population;
- Summary (number and percentage of patients) of the assessment of clinical signs and symptoms of cUTI and AP at each time point throughout the study by treatment group in the MITT Population; and
- Descriptive statistics of the length of hospital stay by treatment group for the MITT Population.

9.2.3 Pharmacokinetic Analysis

Pharmacokinetic characterization and evaluation of serum exposures of ETX2514SUL in the PK Population will be performed using both non-compartmental and modeling methods. Using a sparse sampling approach, PK samples will be obtained from patients treated with either ETX2514SUL or placebo prior to the first dose of study drug on Day 1 (1 sample pre-dose) and at 4 additional time points post-dose of any Day 4 (± 1 day) infusion (4 samples post-dose). The PK samples will be collected for both treatment groups to maintain the blind. The PK samples obtained from the ETX2514SUL group will be analyzed using a validated assay by a central bioanalytical laboratory.

9.2.4 Analysis of Safety

All patients who receive any amount of study drug (Safety Population) will be included in the safety analyses. Patients who received the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received. Safety endpoints include the assessment of TEAEs and the evaluation of changes from baseline in safety laboratory test results, ECGs, vital signs, and physical examinations.

Adverse events will be coded using version 20.0 (or higher) of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients in each treatment group reporting at least 1 occurrence of a TEAE for each unique system organ class and preferred term will be tabulated. A TEAE is defined as an adverse event occurring on or after the administration of the first dose of study drug. Treatment-emergent adverse events will also be tabulated by treatment group, severity, and the relationship to study drug as assessed by the Investigator. The number and percentage of patients in each treatment group reporting at least 1 occurrence of a treatment-emergent SAE will be tabulated. The number and percentage of patients (in each treatment group) prematurely discontinuing study drug treatment due to a TEAE will be tabulated by system organ class and preferred term.

Safety laboratory data will be presented by descriptive statistics of the post-baseline value and the change from baseline, as well as the number and percentage of patients with potentially clinically significant laboratory values. Descriptive statistics of vital signs and ECG parameters and the change from baseline will also be presented. An outlier analysis of the ECG parameters will be conducted.

9.2.5 Interim Analysis

No interim analysis of efficacy has been planned.

9.2.6 Sample Size Determination

Overall, the study is anticipated to randomize approximately 80 patients in a 2:1 ratio to receive ETX2514SUL or placebo. No formal power calculations have been performed for this study. The sample size is based on practical considerations.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the most recent version of the following thesauri will be used:

- MedDRA for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (ie, [REDACTED]) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the Institutional Review Board (IRB) prior to its use and must be in compliance with all International Council for Harmonisation (ICH) GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient and/or legally authorized representative is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient and/or legally authorized representative has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient and/or legally authorized representative before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the patient and/or the patient's legally authorized representative.

11.4 Patient Card

On enrollment in the study, the patient will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki (Seoul 2008) and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs

and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the investigators by ██████████ or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

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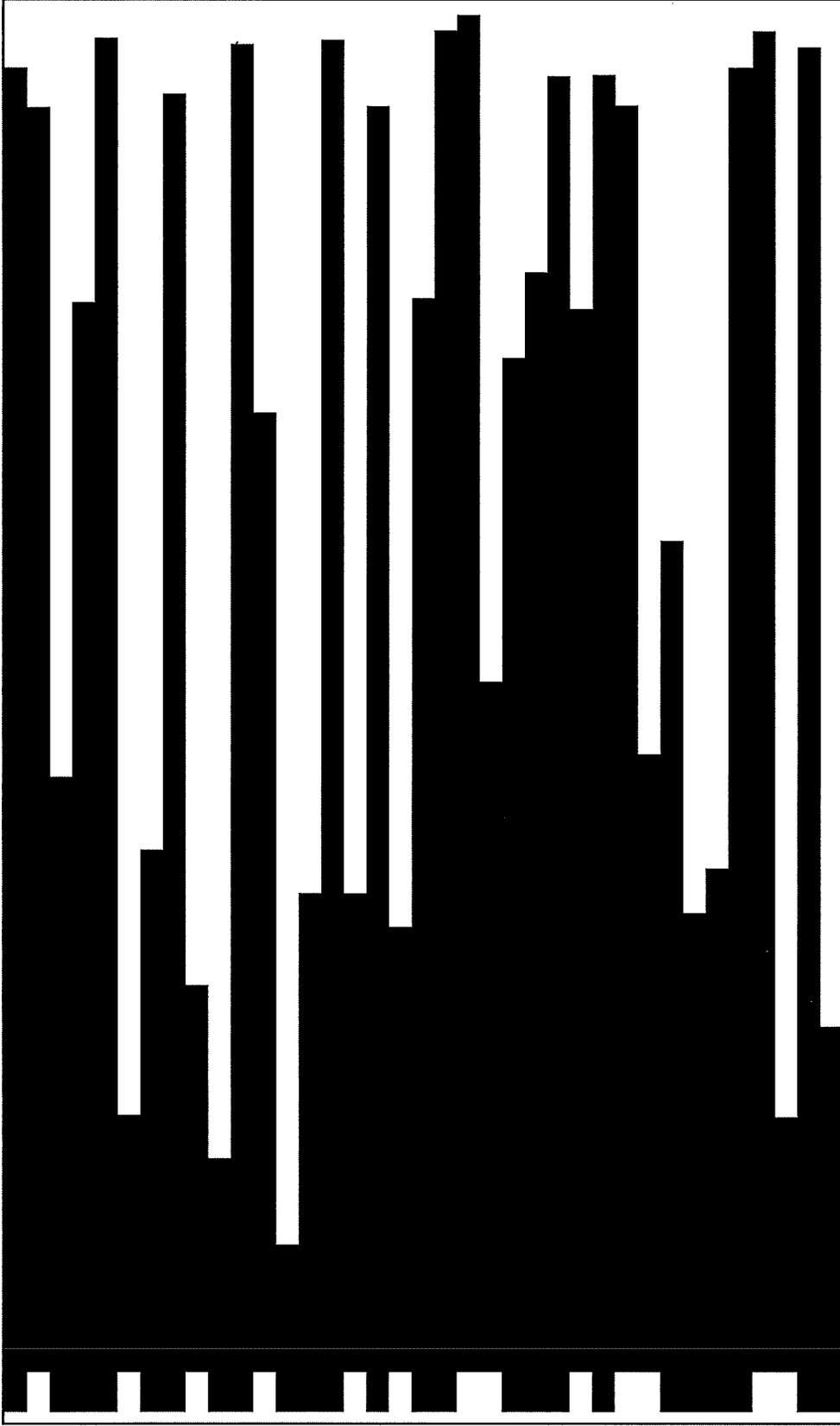
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